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(57) Abstract

Novel complexes of technetium (^{99}Tc or ^{99m}Tc) which contain the moiety Tc=NR, Tc-N=NY or Tc(-N=NY)$_2$, and a ligand which confers biological target-seeking properties on the complex, wherein R represents an aryl group, a substituted or unsubstituted alkyl group, or the grouping =NR^{1}R^2; Y represents an aryl group or a substituted or unsubstituted alky group; and R^1 and R^2 are hydrogen, aryl groups or substituted or unsubstituted aliphatic or cyclic alkyl groups, and may be both the same or different, provided that both are not hydrogen. The complexes are suitable for use in radiopharmaceuticals for a variety of clinical applications. Methods for the preparation of these technetium complexes are also described.

* See back of page

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NEW CORES FOR TECHNETIUM RADIOPHARMACEUTICALS

This invention relates to novel complexes of technetium (Tc), containing the moiety Tc=NR, Tc-N=NY or $Tc(-N=NY)_2$, and their use in radiopharmaceuticals for a variety of clinical applications. Methods for the preparation of the technetium complexes are also described.

Radiopharmaceuticals may be used as diagnostic or therapeutic agents by virtue of the physical properties of their constituent radionuclides. Thus, their utility is not based on any pharmacologic action. Most clinically used drugs of this class are diagnostic agents incorporating a gamma-emitting nuclide which, because of physical or metabolic properties of its co-ordinated ligands, localises in a specific organ after intravenous injection. The resultant images can reflect organ structure or function. These images are obtained by means of a gamma camera that detects the distribution of ionising radiation emitted by the radioactive molecules. The principal isotope currently used in clinical diagnostic nuclear medicine is metastable technetium-99m (^{99m}Tc) and which has a half-life of 6 hours.

The preparation of ^{99m}Tc radiopharmaceuticals generally requires addition of generator-produced $Na^{99m}TcO_4$ eluate to a ligand or ligands in the presence of a reducing agent. Many reducing agents have been used to this effect including tin metal, stannous ion, sodium borohydride, ferrous ascorbate, ferrous ion and formamidine sulphonic acid. These procedures often lead to Tc complexes containing the Tc=O moiety, where the technetium is in the +4 or +5 oxidation state. The formation of such radiopharmaceutical complexes can often occur via

substitution reactions on $[Tc^{V}OX_5]^{2-}$ or $[Tc^{IV}X_6]^{2-}$ molecules, which has been identified as a route of significant synthetic utility (Deutsch E, Libson K, Jurisson S, Lindoy L F, Technetium Chemistry and Technetium Radiopharmaceuticals, Prog. Inorg. Chem. (1982) 30 p 175). Only under harsh reaction conditions in the presence of powerful reducing agents and/or strong acids or bases are Tc^{I} oxidation state complexes attained and stabilised. A limitation to the formation of novel radiopharmaceutical products is the tendency towards formation of Tc = 0 species, but in addition formation of Tc^{4+} or Tc^{5+} complexes also limits the number and/or type of ligands prone to bind to the metal.

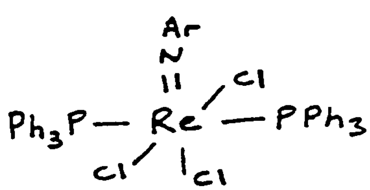
PCT Application WO 85/03063 describes the synthesis of the Tc = N moiety as an intermediate in the preparation of radiopharmaceuticals by virtue of its ability to undergo various ligand substitution reactions. The Tc = N core is again primarily based on the +5 oxidation state of Tc.

The reaction of $TcCl_6^{2-}$ with hydroxylamine salts under a variety of conditions to form a variety of complexes containing the Tc-NO moiety has been described (Eakins, JCS (1963) 6012; Radnovich and Hoard, J. Phys. Chem. 88 (26) (1984) 6713; Armstrong and Taube, Inorg. Chem. (1976) 15 (3), 1904). This literature is concerned with ^{99}Tc and not with its metastable isotope ^{99m}Tc. ^{99}Tc has a half-life of 2.1 x 10^{5} years, decays by emitting beta particles, and is of no interest as a radiopharmaceutical.

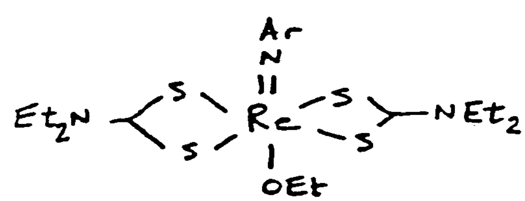
European Patent Application No. 0 291 281 A describes technetium complexes containing the ^{99m}Tc-NO moiety, together with a ligand which confers biological target-seeking properties on the complex, and their use as radiopharmaceuticals. The complexes are made from pertechnetate (TcO_4^-) by a variety of

routes involving hydroxylamine salts. Studies of the coordination chemistry of technetium have generally been directed towards the synthesis and development of new ^{99m}Tc labelled radiopharmaceuticals.[1] The majority of the technetium containing radiopharmaceuticals currently in clinical use involve technetium complexes containing either a mono-oxo or di-oxo core, i.e. $[Tc^{V}=O]^{3+}$ or $[Tc^{V}O_2]^{+}$ respectively.[1,2] Technetium (V) oxo-species are used to image kidney, liver, brain and bone tissues.

The terminal imido (2-) moiety, = NR, is formally isoelectronic to a terminal oxo (2-) function, = O. Many transition metal complexes containing an organo-imido ligand are known[3]. Examples include the following complexes based on rhenium [4,5,6], (I, II), tungsten[7] (III), vanadium[8] (IV) and molybdenum[9] (V):-



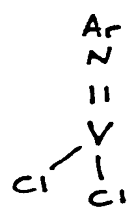
(I)



(II)

$[WCl_4(ArN)]_2$

(III)



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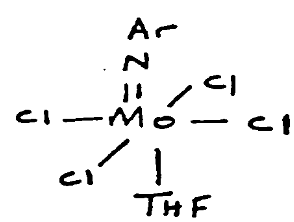
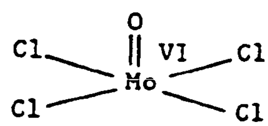


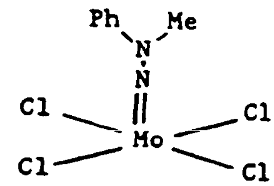
(V)

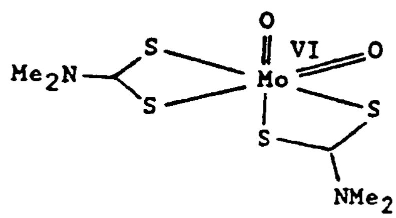
where Ar is an aryl group.

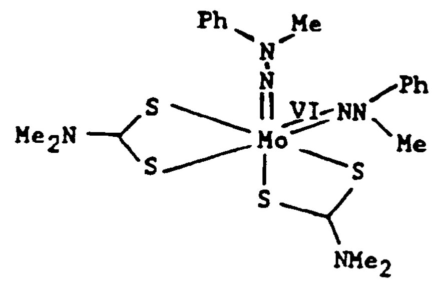
When the R substituent of a terminal imide ligand is a dialkyl amide moiety, NY_2, the imide ligand is more often described as a hydrazide (2-) ligand. Thus the terminal hydrazido (2-) moiety, = N - NR_2, is also isoelectronic to a terminal oxo (2-) function, and many transition metal complexes containing hydrazido (2-) ligands are known[10].

Examples of isostructural metal-oxo and metal-hydrazido (2-) complexes include the following [11,12,13,14]:-









Similarly, the diazenido moiety, - N = NR, is isoelectronic and isostructural with the nitrosyl ligand (- NO).

Unlike oxo- and nitrosyl ligands, however, imide (2-), hydrazido (2-) and diazenido ligands can carry a variety of different substitutents on the nitrogen atom which is not bound to the metal atom. The presence of any of these three moieties in a technetium complex therefore permits the preparation of new radiopharmaceuticals with a variety of biological characteristics which can be modulated by varying or altering the R substituents. In addition, the methods for the synthesis of complexes containing Tc=NR, Tc=N-NY_2 or Tc-N=NY moieties are compatible with the concomitant ligation of a wide variety of other ligands. It is this discovery which forms the basis of the present invention.

According to this invention there is provided a complex of technetium (^{99}Tc or ^{99m}Tc) which contains the moiety Tc=NR, Tc-N=NY or Tc$(-N=NY)_2$, and a ligand which confers biological target-seeking properties on the complex,

wherein R represents an aryl group, a substituted or unsubstituted alkyl group, or the grouping $=NR^1R^2$;

Y represents an aryl group or a substituted or unsubstituted alkyl group;

and R^1 and R^2 are hydrogen, aryl groups or substituted or unsubstituted aliphatic or cyclic alkyl groups, and may be both the same or different, provided that both are not hydrogen.

The complex is useful as a radiopharmaceutical.

Complexes in accordance with this invention have the formulae:

$L_nTc=NR$; $L_nTc-N=NY$ or $L_nTc(-N=NY)_2$

wherein L represents a mono- or multi-dentate ligand;

n is 1, 2, 3 or 4

and R and Y are as defined above.

The alkyl group substituents may be aliphatic (straight chain or branched) or cyclic, and may be substituted with, for example, oxygen, nitrogen, sulphur and/or phosphorus.

A wide range of ligands for these complexes are envisaged, including:-

a) Phosphines and arsines of the general formula $Q_2B(CD_2)_nBQ_2$, where B is P or As; Q is H or aryl or substituted or unsubstituted alkyl, preferably C1 - C4 alkyl or phenyl; n is 1, 2, 3 or 4; and (CD_2) is a substituted or unsubstituted methylene group. Related compounds are described in:-
US 4481184, US 4387087, US 4489054, US 4374821, US 4451450, US 4526776, EP-A-0266910 (Amersham International; methylene bridged diphosphine complexes), EP-A-0311352 (Amersham International; phosphines containing ether groups), and ligands of general type

$$R^3{}_mB\text{-}(CH_2)_n\text{-}W\text{-}(CH_2)_n\text{-}W\text{-}(CH_2)_n\text{-}BR^3{}_m$$

where B is P or As,

W is NR, S, Se, O, P or As,

R^3 is H or hydrocarbon such as C1 - C6 alkyl or aryl,

m is 1 or 2, and

n is 1, 2, 3 or 4.

b) Methylene Diphosphonate (MDP)

c) Thiourea (TU)

d) Thiomalate (TMA)

e) Dimercaptosuccinic acid (DMSA)

f) Gluconate (GLUC)

g) Ethane-1-hydroxy-1,1-diphosphonate (EHDP)

h) Diethylene triamine pentaacetic acid (DTPA)

i) N-(2,6-[Dialkyl]phenyl carbamoylmethyl) iminodiacetate

alkyl = Methyl (HIDA)
Ethyl (EHIDA)
^{i}Propyl (PIPIDA)

j) Dialkyl dithiocarbamate

k) Isonitriles of the general type $C\equiv NR^4$

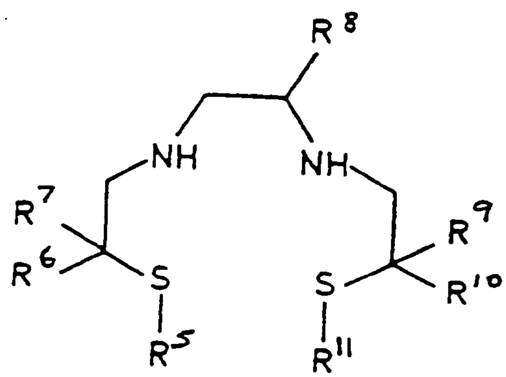
R^4 = alkyl, alkoxy, ether

l) BAT Derivatives - of the general type illustrated below, and specifically:

i) $R^5 = R^{11} = H$
$R^{6,7,9,10} = Et$
R^8 = N-methylspiropiperidinyl

ii) $R^5 = R^{11} = H$
$R^{6,7,9,10} = Et$
R^8 = N-ethylspiropiperidinyl

iii) $R^5 = R^{11} = H$
$R^{6,7,9,10} = Et$
R^8 = N-isopropylspiropiperidinyl

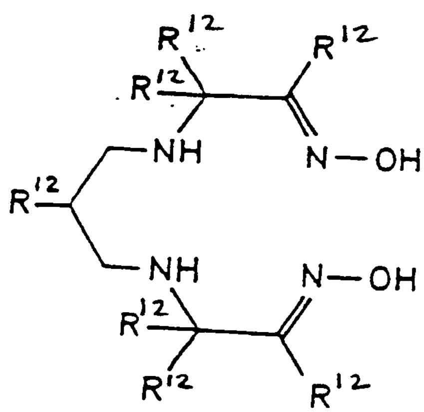


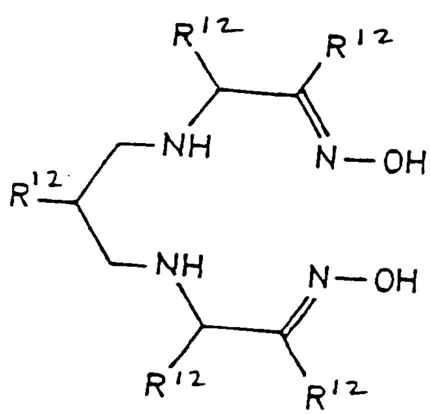
m) phenanthroline,

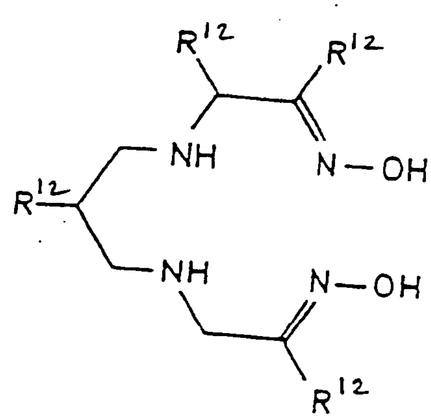
n) pentane-2,4 -dione,

o) bipyridyl,

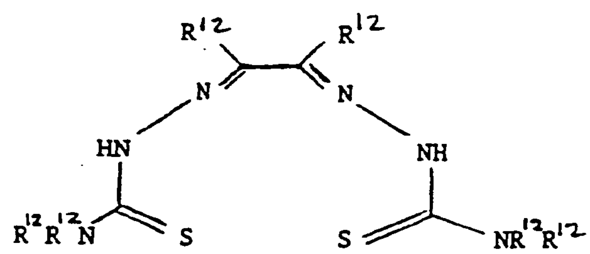
p) Other ligands having propylene amine oxime backbone of the general structural types described in EPA 123504 and 194843:







q) Bisthiosemicarbazones of the formula:



where the various groups R^{12} can be the same or different and are H and/or alkyl and/or aryl substituents. Other suitable ligands are shown in Table 1.

The invention further provides methods for the preparation of the aforementioned complexes of technetium. One such method involves the derivatisation of technetium oxo-containing species by condensation with hydrazines or amines (equation A), isocyanates (equation B), sulphinylamines (equation C) or phosphinimines (equation D):-

A: $L_nTc = O + H_2NR \longrightarrow L_nTc = NR + H_2O$
B: $L_nTc = O + OCNR \longrightarrow L_nTc = NR + CO_2$
C: $L_nTc = O + OSNR \longrightarrow L_nTc = NR + SO_2$
D: $L_nTc = O + Ph_3P = NR \longrightarrow L_nTc = NR + Ph_3P = O$

wherein R, L and n are defined as above. The driving force for these reactions is the formation of a stable product containing the former oxo function (i.e. water, carbon dioxide, sulphur dioxide or phosphine oxide), which is generally easily removed

after the oxo group transfer, leaving the desired technetium hydrazido (2-) or imido complex.

An alternative method of preparation involves the reaction of hydrazines (equation E) or amines (either aliphatic or aromatic) (equation F) with complexes containing technetium-halogen bonds:-

$$E:\ L_nTc\ Cl_2 + H_2NNR^1R^2 \longrightarrow L_nTc = NNR^1R^2 + 2HCl$$
$$F:\ L_nTc\ Cl_2 + H_2NR \longrightarrow L_nTc = NR + 2HCl$$

where L, R, R^1 and R^2 are as previously defined.

The driving force for these reactions is the concomitant formation of the volatile, easily removed hydrogen halide during the metathesis reaction.

It will be appreciated that the hydrazides and diazenides can be considered as essentially being functionalised imide ligands. The hydrazide (2-) ligand, $=NNR^1R^2$, is just the imide ligand, =NR, where R is NR^1R^2; and the diazenide ligand results when R_1 is hydrogen. In this case, the intermediate hydrazide (2-) complex is deprotonated by a base to give a metal-diazenide complex with concomitant reduction of the metal centre:

$$M^{n+} - N\text{-}NHR^2 \xrightarrow{B:} [\ M - N - N(H)R^2\ ]\ :B \longrightarrow M^{(n-2)+}N - N - R^2$$

In the reactions reported herein, the base is always the added excess of hydrazine in the solution.

Turning now to the preparation of the technetium complexes containing an imido moiety, the approach has been to replace the oxo function in

$[TcOX_4]^-$ (X = Cl, Br) using arylisocyanates (reaction type equation B). This formed a convenient entry point into the work by extending an established route for the synthesis of Tc=NR complexes. This method has only been previously used for generation of neutral imido products from neutral transition metal oxo starting materials.[17] The work reported here is thus the first example of the method extended to the preparation of anionic transition metal imido complexes, and also to technetium chemistry.

Reaction of $[Tc^{V}OX_4]^-$ with excess ArNCO in refluxing dry toluene under nitrogen gives excellent yields of the desired Tc^{V}-imido products isolated as solids on ether trituration of the residue obtained directly from the reaction mixture (equation G):-

$$\text{G:}\quad (Bu_4N)\,[TcOX_4] + \text{excess MePhNCO} \xrightarrow{\text{toluene, reflux}} (Bu_4N)\,[Tc(Ntol)X_4]$$

X = Cl, 95-100 % <u>1</u>
X = Br, 74 % <u>2</u>

Even though the method gives good yields of reasonably pure solids, the reaction is <u>not</u> trivial. The starting isocyanates are quite moisture and air sensitive such that the reaction must be strictly performed under an atmosphere of N_2. <u>1</u> and <u>2</u> are black-blue solids that are also quite sensitive to adventitious moisture, however, they are stable under dry N_2. That the products are very sensitive to moisture is evidenced by the fact that if reagent grade diethyl ether is used in the trituration phase of the workup procedure instead of anhydrous ether, then the

product is isolated as a red-brown insoluble polymeric compound. The products also do not always chromatograph (HPLC) satisfactorily.

The products $[Tc(Ntol)X_4]^-$ contain the new core moiety $[Tc^V{=}NR]^{3+}$ which is formally analogous to the well known $[Tc{=}O]^{3+}$ core[1]. $[Tc(NR)X_4]^-$ is a sixteen electron species in which the imido ligand functions as a four electron donor; the technetium-nitrogen bond is therefore expected to be a short, linear multiple [Tc=NR] bond. Attempted structural characterisation of $[Tc(Ntol)Cl_4]^-$ as its PPh_4^+ salt by X-ray crystallography has so far been unsuccessful due to its sensitive nature. The products <u>1</u> and <u>2</u> are very good starting materials for the preparation of many new Tc=NR complexes.

In view of the somewhat sensitive nature of <u>1</u> and <u>2</u>, investigation of much more stable Tc-imido complexes was undertaken. The direct metathesis reactions of $[TcOCl_4]^-$ with aromatic amines was undertaken in the presence of phosphine ligands. Reactions of this type may show promise in ^{99m}Tc chemistry in view of the wide variety of substituted aromatic amines available commercially.

Reaction of $[TcOCl_4]^-$ with $ArNH_2$ in refluxing MeOH in the presence of the monodentate phosphine PPh_3 gives the green-brown neutral Tc^V imido complexes which analyse for $[Tc(NR)Cl_3(PPh_3)_2]$ (equation H):-

H: $$(Bu_4N)[TcOCl_4] + \text{excess } ZC_6H_4NH_2 + \text{excess } PPh_3 \xrightarrow{\text{MeOH, reflux}} [Tc(NC_6H_4Z)Cl_3(PPh_3)_2]$$

<u>3</u> $Z = CH_3$
<u>4</u> $Z = Br$
<u>5</u> $Z = Cl$

Chromatographic analysis (HPLC, beta detection) of these products show only one significant ^{99}Tc-containing species. These neutral Tc^{V} complexes also contain the new $[Tc^{V}=NR]^{3+}$ core. They are diamagnetic, air-stable solids which are very soluble in CH_2Cl_2, $CHCl_3$, moderately soluble in alcohols, and insoluble in ether and petrol. They exhibit a singlet (<u>ca.</u> 30 ppm) in the ^{31}P NMR spectrum, indicating two <u>trans</u>-PPh_3 groups in identical environments. Structural characterisation of <u>3</u> by X-ray has now been carried out and Figure 1 gives a Ball and Stick representation of the complex molecule. The diagram shows a linear tolylimide group and the two PPh_3 groups to be <u>trans</u>. The [Tc=Ntol] unit in <u>3</u> may therefore be correctly assigned as a linear four electron donor imido ligand, and the complex is formally an 18-electron species.

This work therefore represents the first structurally characterised Tc^{V}-imido complex.

The $[Tc(NR)Cl_3(PPh_3)_2]$ compounds are much superior starting materials than $[Tc(NR)X_4]^-$ because these are much more stable Tc=NR species.

Reaction of $[TcOCl_4]^-$ with excess amine and dppe in refluxing MeOH or EtOH allows the isolation of good yields of the cationic Tc-imido complexes $[Tc^{IV}(NC_6H_4Z)Cl-(dppe)_2]^+$ as their BPh_4^- salts (equation I):-

I: $(Bu_4N)[TcOCl_4]$ + excess $ZC_6H_4NH_2$ + excess dppe

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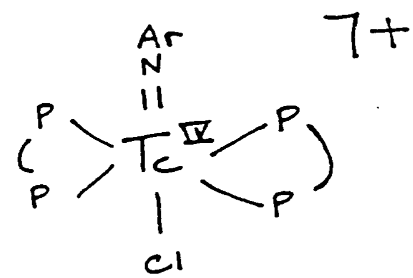


<u>6</u> Z = CH_3, 60 %, violet

<u>7</u> Z = Br, 64 %, maroon

<u>8</u> Z = Cl, 64 %, maroon

These complexes 6,7, and 8 are all air-stable darkly coloured cationic Tc^{IV}-imido complexes. Chromatographic analysis (HPLC, beta detection) indicates single ^{99}Tc-containing species. They are quite soluble in CH_2Cl_2 and insoluble in ether, petrol and alcohols. They may be conveniently recrystallised from CH_2Cl_2/MeOH.

Their assignment as Tc(IV) complexes is from the following characterisation: The analysis stoichiometry fits the formula $[Tc(NR)Cl(dppe)_2](BPh_4)$. Although ν Tc=N is not assignable there is no evidence for ν NH in the infrared. The compounds exhibit very broadened NMR spectra (^1H, ^{31}P) at room temperature which are not easily assigned. They are assumed to be paramagnetic Tc^{IV} imido complexes and not Tc^{III}-amido (TcNHR) complexes on this basis.

This represents another new core, the $[Tc^{IV}=NR]^{2+}$ moiety. Evidence for the existence of this new Tc^{IV} core comes from the structural characterisation of a $[Tc^{IV}$-hydrazido(2-)bis(dppe)Cl$]^+$ cation which contains a $[Tc^{IV}NNR_2]^{2+}$ core[18]. Hydrazido(2-) and imido(2-) are formally analogous. Further evidence comes from the existence and relative stability of the analogous $[Tc^{IV}=O]^{2+}$ core from the electrochemical reduction of some Tc^{V} oxo Schiff base complexes[19].

It is to be understood that reactions of the aforementioned type A-F are well known for the synthesis of various transition metal hydrazido (2-) and imido complexes[3,10]. While it is believed that they have not previously been used for the production of technetium complexes of the kind described and claimed herein, it is acknowledged that the synthesis of technetium-nitride complexes using hydrazine hydrochloride itself has already been reported[15,16].

Using the approach of equation A above, the reactions of hydrazines with $[NBu_4][TcOCl_4]$ were studied, and the intermediate products further

functionalised with mono- or bi-dentate ligands. In particular, the reaction of complexes containing technetium-oxo moieties [Tc=O] with mono-substituted hydrazines or 1,1-disubstituted hydrazines produces technetium-diazenide or technetium-hydrazide (2-) species.

The facile synthesis of $[TcCl(NNPh)_2(PPh_3)_2]$ from $[Bu_4N][TcOCl_4]$, $PhNHNH_2$, and PPh_3 in methanol under reflux has been demonstrated.[25] This complex proved to be somewhat insoluble and could not be satisfactorily recrystallised due to its poor solubility. This unsubstituted phenyl-diazenido-complex thus appears to be polymeric, possibly containing chloro- bridges. Consequently it was not thought to be a suitable starting material for investigation of substitution chemistry.

Use of 4-substituted hydrazine hydrochlorides $4\text{-}XC_6H_4NHNH_2.HCl$ (X = Cl, CH_3) has lead to the preparation of the analogous bisdiazenido- complexes $[TcCl(NNC_6H_4X)_2(PPh_3)_2]$ (X = Cl, 9; X = CH_3, 10). These air-stable orange crystalline solids are reasonably soluble compounds and are much superior starting materials. Complex 9 (X = Cl) in particular has proved to be the most suitable for a systematic investigation of the substitution chemistry of the technetium bis diazenido- complexes, giving relatively clean products on reaction with the appropriate ligand.

A most important development in this work is the fact that these diazenido- complexes $[TcCl(NNR)_2(PPh_3)_2]$ may also be synthesised directly from $[TcO_4]^-$. Reaction of $[NH_4][TcO_4]$ with $ClC_6H_4NHNH_2.HCl$ and PPh_3 in dry methanol under reflux gives a good (60-70%) yield of $[TcCl(NNC_6H_4Cl)_2(PPh_3)_2]$ 9. Many variations in experimental conditions were tried. The best method

is reported here. This result suggests that all technetium diazenido- complexes may be synthesised in good yield directly from $[TcO_4]^-$.

In order to investigate which complexes could be synthesised directly from $[TcO_4]^-$ in future work, it has been important to demonstrate that the diazenido- (and imido-) cores may be incorporated into a wide variety of complex types. For diazenido- cores this has mainly been approached by the systematic substitution of 9.

Reaction of 9 with excess dppe in methanol under reflux gives pure $[TcCl(NNC_6H_4Cl)(dppe)_2]^+$, 12 isolated as orange crystalline BPh_4^- or PF_6^- salts in good yield. Complexes of this type may also be prepared directly from $[NH_4][TcO_4]$.

Reaction of 9 with dmpe under similar conditions leads to the isolation of a pale-pink cationic solid (HPLC retention time 10 minutes, single species) containing no nitrogen. This product could not be isolated in pure form, but is tentatively formulated as $[Tc^I(dmpe)_3][BPh_4]$. The analogous reaction under less forcing conditions at room temperature leads to the desired cation $[TcCl(NNC_6H_4Cl)(dmpe)_2]^+$ isolated as its PF_6^- salt (HPLC retention time 9.6 minutes, single species).

In order to elucidate the validity of both $[Tc(N_2Ar)_2]^+$ and $[Tc(N_2Ar)]^{2+}$ as new cores for the development of Tc-based radiopharmaceutical products it was necessary to investigate the lability of the $-N_2Ar$ unit on reaction with other ligands. Detailed HPLC experiments (beta detection) were performed to see if a bis diazenido- intermediate was

formed in the preparation of the cation 12 (retention time 14 minutes) from the starting material 9 (retention time 9.4 minutes). The HPLC results showed that the cation formed after only 15 minutes stirring at room temperature, and that no other Tc-containing intermediate was detected. This proves that one $-N_2Ar$ moiety is very labile, and is easily lost in solution at room temperature in the presence of the appropriate ligand to give the monodiazenido- product.

Reaction of 9 and 10 with the less bulky phosphines (PMe_2Ph, $PMePh_2$) gave single species in solution (HPLC). However, the high solubility precluded further workup of these apparently cationic products. Reaction of $[Bu_4N][TcOCl_4]$, $XC_6H_4NHNH_2.HCl$ (X = Cl, CH_3) and the appropriate phosphine also leads to isolation of these solutions (HPLC).

Reaction of the commercially available hydrazine $O_2NC_6H_4NHNH_2$ with $[Bu_4N][TcOCl_4]$ and PPh_3 in methanol leads to the isolation of the lime-green Tc(III) monodiazenido-complex $[TcCl_2(NNC_6H_4NO_2)(PPh_3)_2]$, 11 in reasonable yield. Apparently a bis diazenido- complex is not formed from reaction of this nitro-substituted phenylhydrazine. The complex 11 promises to be a useful starting material for the preparation of a variety of monodiazenido- complexes as it has two easily replaceable chlorides. In the presence of dppe in methanol-toluene under reflux complex 11 gives orange $[TcCl(NNC_6H_4NO_2)(dppe)_2]^+$, 13 isolated as its BPh_4^- salt in good yield. $[TcCl(NNC_6H_4NO_2)(dmpe)_2][PF_6]$ (retention time 10

minutes, single species) was prepared in high yield directly from $[TcOCl_4]^-$, the hydrazine, and dmpe in refluxing methanol-toluene.

Reaction of 9 with sodium dimethyldithiocarbamate in absolute ethanol under reflux gives the novel orange Tc(III) diazenido- complex $[Tc(NNC_6H_4Cl)(S_2CNMe_2)_2(PPh_3)]$, 14 in reasonable (66%) yield. Complex 14 is air-stable both in the solid state and in solution. Recrystallisation from CH_2Cl_2/Et_2O gives X-ray quality orange crystals. Satisfactory elemental analysis and spectroscopic data suggest the formulation to be correct. The room temperature ^1H NMR spectrum of 14 is indicative of its coordination geometry. The four methyl groups in 14 appear as four sharp singlets. This resonance pattern shows that the two dithiocarbamato ligands are non-equivalent, and is consistent with a cis-conformation. This has to be confirmed by X-ray structure analysis. If the dithiocarbamato ligands were trans- and the four methyl groups thus equivalent, the ^1H spectrum would show a single resonance which would not be expected to change with temperature.

Reaction of 9 with maltol gives a dark-orange crystalline compound. This is a single species (HPLC) and analyses as $[TcCl(NNC_6H_4Cl)(maltol)(PPh_3)_2]$, 15. This novel Tc(III) diazenido complex is formally analogous to the structurally characterised $[ReCl(NNCOPh)(maltol)(PPh)_3)_2]$[26], and is the first reported Tc complex containing the maltol ligand.

Reaction of 9 with the tetradentate $N_2O_2(2-)$ ligand salenH_2 in methanol-toluene under reflux in the presence of Et_3N gives the neutral dark-green Tc(III) diazenido- complex $[Tc(NNC_6H_4Cl)(salen)(PPh_3)]$, 16 in good yield. Similar reaction of 9 with the obligately planar tetradentate $N_2O_2(2-)$ ligand salphenH_2 gave no well defined product suggesting that a *cis*-geometry of the $-N_2Ar$ and PPh_3 groups is preferred. Further evidence for a preferred *cis*-geometry is suggested from the spectroscopic results of 14. This is expected to be confirmed by X-ray structure analysis.

Reaction of 9 with the N_2S_2 ligand $(HSCH(Me)CONHCH_2-)_2$ in the presence of Et_3N gave a dark-brown solid. The product was too insoluble for satisfactory analysis by NMR, but appeared to be diamagnetic. Elemental analysis on the product isolated directly from the reaction mixture suggested the formulation as a bis diazenido- complex $[Tc(NNC_6H_4Cl)_2-(SCH(Me)CONHCH_2CH_2NHCOCH(Me)S)]_x$, 17.

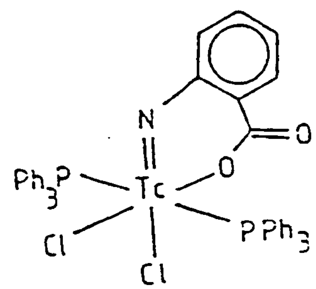
Much effort has been directed to the development of a

synthetic route to Tc imido- complexes directly from $[TcO_4]^-$. Reaction of aqueous methanolic solutions of $[TcO_4]^-$ with aromatic amine and PPh_3 in the presence of concentrated HCl gives only low yields of the desired Tc(V) imido- complexes $[TcCl_3(NAr)(PPh_3)_2]$. These complexes have been prepared previously from $[Bu_4N][TcOCl_4]$.[25] The nature of the reaction from $[TcO_4]^-$ appears to be very dependent on the concentration of HCl used. Use of excess HCl gives $[TcCl_4(PPh_3)_2]$.

The use of amine hydrochloride ($ArNH_3Cl$) as an alternative to the addition of HCl in this reaction has also been investigated in some detail. $[TcO_4]^-$ reacts with $ArNH_3Cl$ and PPh_3 in aqueous methanol to give a bright blue, neutral product in high yield after about 20 minutes stirring at room temperature. This product appears to be independent of the aromatic amine hydrochloride used. The blue compound appears to be diamagnetic (NMR) and shows evidence for coordinated PPh_3, but contains no nitrogen. This compound analyses reasonably as $[Tc_2Cl_4(PPh_3)_4]$ which is analogous to many known Re-Re multiply bonded species. Use of aliphatic amine hydrochlorides (RNH_3Cl) leads to rapid conversion to black insoluble "$TcO_2.xH_2O$".

Reaction of $[NH_4][TcO_4]$ with the hydrochloride of anthranilic acid ($2\text{-}HO_2CC_6H_4NH_3Cl$) under analogous conditions gives a lime-green precipitate. This analyses reasonably well as $[TcCl_2(NC_6H_4CO_2)(PPh_3)_2]$, <u>18</u> and is expected to have the novel structure containing a bent TcN framework. The bent chelating imidobenzoate(3-) ligand is thus a new core moiety for technetium. The complex <u>18</u> may also be prepared from $[TcOCl_4]^-$ in lower yield. Anthranilic acid is known to react

with $[ReOCl_3(PPh_3)_2]$ in ethanol to give the chelating imidobenzoate(3-) complex $[ReCl(OEt)(NC_6H_4CO_2)(PPh_3)_2]$.[27]



18

This is a major development as it suggests that imido- complexes are more generally accessible from $[TcO_4]^-$. The chelate effect must in some way stabilise the formation of this imido- ligand. The establishment of a conjugation pathway through the M=N, C=C, and C=O may be a driving force for its formation. The reaction of $[TcO_4]^-$ and anthranilic acid hydrochoride in the presence of a wide variety of non-phosphine ligands is envisaged.

Much effort has been directed to synthesis of Tc imido- ligands from $[TcO_4]^-$ using the hydrazines RCONHNHAr (R = CH_3, Ph), and also their hydrochlorides as a source of the NAr ligand. Use of the symmetrically substituted hydrazines RNHHNR (R = Me, Et, PhCO, Ph) is also envisaged. Preliminary experiments for both $[TcO_4]^-$ and $[TcOCl_4]^-$ have shown that mixtures of products are being formed (HPLC).

Our work has resulted in the synthesis of two new classes of technetium complexes with hydrazido (2-), i.e. $^{=}NNR_2$, and diazenido, i.e. -NNR, substituents, at both the carrier added (^{99}Tc) and the no carrier added (^{99m}Tc) levels. Both neutral and cationic derivatives have been prepared within each class. These complexes are useful as radiopharmaceuticals and thus provide a new range of such reagents.

Specifically, the following new complexes containing hydrazido (2-) and diazenido moieties have been prepared:-

^{99}Tc: Carrier Added Level

$[Tc^{V}(NNMePh)Cl_3(PPh_3)_2]$
$[Tc^{V}(NNMePh)Cl_2(PMe_2Ph)_3][PF_6]$
$[Tc^{V}(NNMePh)Cl(Et_2NCS_2)_2]$
$[Tc(N_2)Cl(dppe)_2]$
$[Tc^{IV}(NNMe_2)Cl(dppe)_2][PF_6]$
$[Tc^{V}O(NH)dppe][PF_6]$
$[Tc^{III}(NNPh)_2Cl(PPh_3)_2]$
$[Tc^{III}(NNPh)Cl(dppe)_2][PF_6]$
$[Tc(NNC_6H_4Cl)Cl(dppe)_2)[PF_6]$
$[Bu_4N][Tc(NC_6H_4CH_3)Br_4]$, $[Bu_4N][Tc(NC_6H_4CH_3)Cl_4]$, $Tc(NC_6H_4Z)Cl_3(PPh_3)_2$ where Z = CH_3, Br, Cl,
$[Tc(NC_6H_4Z)Cl(dppe)_2][BPh_4]$, where Z is as above.

^{99m}Tc: No-Carrier Added Level*

$[Tc^{III}(NNPh)Cl(L)_2]^+$
L = dmpe, dppe, P46, P53, P56, P68, PL28, PL31, PL34, PL37, PL38, PL40, PL42, PL43, PL46, PL49, PL50.

$[Tc^{III}(NNC_6H_4NO_2)Cl(L)_2]^+$
L = dmpe
$[Tc^{IV}(NNMePh)Cl(L)_2]^+$
L = dmpe, P34, P46, P53, P65, P68, PL28, PL38

* The structures of the ligands, L, given here are shown in Table 1.

Of these, animal biodistribution data has been obtained for the following ^{99m}Tc species and the results are shown in Tables 2, 3 and 4:-

$[Tc^{III}(NNPh)Cl(L)_2]^+$
L = dmpe, PL28, P46, PL42, PL43, P65, PL50, PL38 (Table 2)

$[Tc^{III}(NNC_6H_4NO_2)Cl(L)_2]^+$
L = dmpe (Table 3)

$[Tc^{IV}(NNMePh)Cl(L)_2]^+$
L = dmpe, P46, P65 (Table 4)

This invention will now be further illustrated by the following Examples:-

<u>^{99}Tc Complexes</u>

All reactions were performed under an atmosphere of nitrogen using predried, distilled solvents unless noted otherwise. $[NBu_4][TcOCl]$ was prepared by the literature procedure[20]. All other reagents used were obtained from commercial sources and used as received. Aqueous solutions of $[NH_4][TcO_4]$ were obtained from Amersham International plc.

All complexes were characterised by elemental analysis, IR, ^1H NMR and ^{31}P NMR. Only analytical data are included here but spectroscopic information is available. In addition to the above physical characterisation of the complexes single crystal X-ray structures have been obtained for four complexes: $[Tc(NNPh)Cl(dppe)_2][PF_6]$, $[Tc(NH)O(dppe)_2][PF_6]$, $[Tc(NNMe_2)Cl(dppe)_2][PF_6]$ and $Tc(NC_6H_4CH_3)Cl_3(PPh_3)_2$.

Example 1

Reaction of $(Bu_4N)[TcOX_4]$ (X = Cl, Br) with 4-Tolyl-isocyanate

i) Tetrabutylammonium(1+)tetrachloro(p-tolylimido) technetate (V) (1-), $(Bu_4N)[Tc(Ntol)Cl_4]$ 1

$(Bu_4N)[TcOCl_4]$ (0.194 g, 0.39 mmol) was suspended in dry degassed toluene (10 ml) and MePhNCO (0.25 ml, 1.98 mmol, 5 equivalents) was added. The mixture was then vigorously refluxed under N_2 for 45 minutes. After cooling to room temperature the toluene was decanted off, and the black residue was triturated with dry diethyl ether (10 ml) before collection of the blue-black solid 1 by filtration. On washing thoroughly with diethyl ether the product was dried *in vacuo*. (Yield 0.229 g, 0.39 mmol, 100%). In similar preparations of 1 the yield was never less than 95% and therefore the conversion was considered to be essentially quantitative. (Found: C, 49.31; H, 7.22; N, 5.02. calc for $TcC_{23}H_{43}N_2Cl_4$: C, 47.03; H, 7.37; N, 4.77%); ^1H NMR (d_6-DMSO) 0.9[12H, broad unresolved triplet, $(C\underline{H}_3(CH_2)_3)_4N$]; 1.4[24H, broad multiplet, $(CH_3(C\underline{H}_2)_3)_4N$]; 2.2[3H, singlet, $C\underline{H}_3C_6H_4N$-Tc]; 7.0-7.4[4H, multiplet, $CH_3C_6\underline{H}_4NTc$]; $v_{max.}$ (Nujol mull, KBr plates) 1170 m br cm^{-1} (Tc=N, tentative assignment).

ii) Tetrabutylammonium(1+)tetrabromo(p-tolylimido) technetate (V) (1-), $(Bu_4N)[Tc(Ntol)Br_4]$ 2

The blue-black product 2 was prepared in a similar

fashion to 1 using $(Bu_4N)[TcOBr_4]$ (0.268 g, 0.396 mmol) and MePhNCO (0.25 ml, 1.98 mmol, 5 equivalents) in refluxing dry toluene (15 ml). (Yield 0.224 g, 0.29 mmol, 74%). HPLC retention time 9.6 minutes, single species; (Found: C, 36.73; H, 6.43; N, 3.16. calc for $TcC_{23}H_{43}N_2Br_4$: C, 36.10; H, 5.66; N, 3.66%); ^1H NMR ($CDCl_3$) 1.0[12H, broad unresolved triplet, $(C\underline{H}_3(CH_2)_3)_4N$]; 1.5[24H, broad multiplet, $(CH_3(C\underline{H}_2)_3)_4N$]; 2.27[3H, singlet, $C\underline{H}_3C_6H_4NTc$]; 6.9-7.5[4H, multiplet, $CH_3C_6\underline{H}_4NTc$]; $\nu_{max.}$ (Nujol mull, KBr plates) 1175 cm^{-1} (Tc=N, tentative assignment).

Example 2

Reactions of $(Bu_4N)[TcOCl_4]$ with Aromatic Amines ($4-ZC_6H_4NH_2$, Z = CH_3, Br, Cl) in the Presence of Triphenylphosphine, PPh_3

i) Trichloro(p-tolylimido)bis(triphenylphosphine) technetium (V), $Tc(NC_6H_4Z)Cl_3(PPh_3)_2$ Z = CH_3, 3

$(Bu_4N)[TcOCl_4]$ (0.216 g, 0.43 mmol), $CH_3C_6H_4NH_2$ (0.07 g, 0.65 mmol, 1.5 equivalents) and PPh_3 (0.34 g, 1.3 mmol, 3 equivalents) were refluxed in dry methanol (10 ml) under N_2 for 40 minutes. After cooling to room temperature, the brown-green mixture was evaporated to 5 ml, and diethyl ether (15 ml) was added to aid precipitation of 3. The green-brown product was collected by filtration, washed thoroughly with ether and dried. The product could be recrystallised from CH_2Cl_2/hexane mixture. (Yield 0.094 g, 0.11 mmol, 26%). HPLC retention time 10.8 minutes, single species; (Found: C, 59.01; H, 4.35; N, 1.76; Cl, 12.80. calc for $TcC_{43}H_{37}NCl_3P_2$: C, 61.84; H, 4.46; N, 1.68; Cl, 12.74%); ^1H NMR ($CDCl_3$) 2.2[3H,

s, $C\underline{H}_3C_6H_4NTc$]; 6.5-6.8[4H, m, $CH_3C_6\underline{H}_4NTc$]; 7.0-8.0[30H, m, phenyl H]. There was no evidence of NH in the proton spectrum; $^{31}P-\{^1H\}$ NMR ($CDCl_3$) 30.02 s ppm; $v_{max.}$ (Nujol mull, KBr plates) 1165 cm^{-1} (Tc=N, tentative assignment). There were no absorptions which could be attributed to v_{NH}.

ii) Trichloro(p-bromophenylimido)bis(triphenylphosphine) technetium (V), $Tc(NC_6H_4Z)Cl_3(PPh_3)_2$ Z = Br, 4

(Bu_4N) [$TcOCl_4$] (0.210 g, 0.42 mmol), $BrC_6H_4NH_2$ (0.11 g, 0.64 mmol, 1.5 equivalents) and PPh_3 (0.331 g, 1.26 mmol, 3 equivalents) were refluxed in dry methanol (10 ml) to give on workup and recrystallisation from CH_2Cl_2/hexane a very low yield of brown solid 4. (Yield 0.052 g, 0.06 mmol, 14%). HPLC retention time 9.6 minutes, single species; (Found: C, 54.38; H, 4.00; N, 1.53; Cl, 10.56. calc for $TcC_{42}H_{34}NP_2Cl_3Br$: C, 56.05; H, 3.81; H, 1.56; Cl, 11.82. calc for $TcC_{42}H_{34}NP_2Cl_3Br.1/2\ CH_2Cl_2$: C, 54.45; H, 3.72; N, 1.48; Cl, 14.95%); ^1H NMR ($CDCl_3$) 5.25[s, $C\underline{H}_2Cl_2$]; 6.8[4H, m, $BrC_6\underline{H}_4NTc$]; 7.0-8.0[30H, m, phenyl H]; $^{31}P-\{^1H\}$ NMR ($CDCl_3$) 29.93 s ppm; $v_{max.}$ (Nujol mull, KBr plates) 1165 cm^{-1} (Tc=N, tentative assignment).

iii) Trichloro(p-chlorophenylimido)bis(triphenylphosphine) technetium (V), $Tc(NC_6H_4Z)Cl_3(PPh_3)_2$ Z = Cl, 5

(Bu_4N)[$TcOCl_4$] (0.272 g, 0.545 mmol), $ClC_6H_4NH_2$ (0.104 g, 0.82 mmol, 1.5 equivalents) and PPh_3 (0.43 g, 1.64 mmol, 3 equivalents) were refluxed in dry methanol (10 ml) to give a very low yield of brown solid 5. (Yield 0.084 g, 0.098 mmol,

18%). HPLC retention time 9.2 minutes, single species; (Found: C, 55.85; H, 3.86; N, 1.63. calc for $TcC_{42}H_{34}NP_2Cl_4$: C, 58.96; H, 4.00; N, 1.64%); ^1H NMR ($CDCl_3$) 6.5-6.7[4H, m, $ClC_6\underline{H}_4NTc$]; 7.0-8.0[30H, m, phenyl H]; ^{31}P-{^1H} NMR ($CDCl_3$) 29.87 s ppm; $v_{max.}$ (Nujol mull, KBr plates) 1170 cm^{-1} (Tc=N, tentative assignment.

<u>Example 3</u>

<u>Reactions of $(Bu_4N)[TcOCl_4]$ with Aromatic Amines (4-$ZC_6H_4NH_2$, Z = CH_3, Br, Cl) in the Presence of Bis(diphenylphosphino)ethane, dppe</u>

i) $[Tc(NC_6H_4Z)Cl(dppe)_2](BPh_4)$ Z = CH_3, <u>6</u>

$(Bu_4N)[TcOCl_4]$ (0.333 g, 0.67 mmol), $CH_3C_6H_4NH_2$ (0.36 g, 3.33 mmol, 5 equivalents), and dppe (0.80 g, 2.0 mmol, 3 equivalents) in dry degassed methanol (20 ml) were refluxed for 1 hour. After cooling to room temperature, the violet mixture was filtered into a clean flask to remove some insoluble red material. Sodium tetraphenylborate (0.23 g, 0.67 mmol) in methanol (5 ml) was added with stirring to immediately precipitate out a copious amount of violet solid <u>6</u>. The product was collected by filtration and washed thoroughly with MeOH, and then ether. The product could be recrystallised from CH_2Cl_2/MeOH or CH_2Cl_2/hexane. (Yield 0.544 g, 0.40 mmol, 60%). HPLC retention time 8.4 minutes, one major species; (Found: C, 74.09; H, 7.09; N, 1.70; Cl, 3.22. calc for $TcC_{83}H_{75}NClP_4B$: C, 73.54; H, 5.58; N, 1.03; Cl, 2.62%).

There are no infrared absorptions assignable to NH stretches, and the ^{v}Tc=N stretch could not be assigned unambiguously. The product gave a broadened ^1H NMR spectrum and was assumed to be paramagnetic Tc(IV). The ^{31}P NMR spectrum also showed broadened resonances.

If less $ArNH_2$ was used in the reaction a red precipitate believed to be $[Tc^{III}Cl_2(dppe)_2]Cl$ forms in approximately 50% yield from the MeOH on cooling to room temperature.

ii) $[Tc(NC_6H_4Z)Cl(dppe)_2](BPh_4)$ Z = Br, 7

$(Bu_4N)[TcOCl_4]$ (0.179 g, 0.36 mmol), $BrC_6H_4NH_2$ (0.31 g, 1.79 mmol, 5 equivalents) and dppe (0.429 g, 1.08 mmol, 3 equivalents) were refluxed in dry methanol (10 ml, 1 hour). $NaBPh_4$ (0.122 g, 0.36 mmol) in MeOH (5 ml) was added to the cooled filtered reaction mixture with stirring to isolate 7 as a maroon solid on filtration. (Yield 0.325 g, 0.23 mmol, 64%). HPLC retention time 7.6 minutes, one major species. Analysis on the crude material gave (Found: C, 73.19; H, 5.91; N, 0.89; Cl, 3.19. calc for $TcC_{82}H_{72}NBrClP_4B$: C, 69.33; H, 5.11; N, 0.99; Cl, 2.50%) and suggests contamination with BPh_4^- or Cl^-. The product could be recrystallised from CH_2Cl_2/MeOH.

iii) $[Tc(NC_6H_4Z)Cl(dppe)_2](BPh_4)$ Z = Cl, 8

$(Bu_4N)[TcOCl_4]$ (0.28 g, 0.56 mmol), $ClC_6H_4NH_2$ (0.358g, 2.8 mmol, 5 equivalents) and dppe (0.67 g, 1.68 mmol, 3 equivalents) were refluxed in dry methanol (15 ml, 75 minutes). $NaBPh_4$ (0.19 g, 0.56 mmol) in MeOH (5 ml) was added to the cooled filtered reaction mixture with stirring to precipitate out the dark maroon solid 8 which was collected by filtration. (Yield 0.497 g, 0.36 mmol, 64%). HPLC retention time 8.0 minutes, one major species. Analysis on the crude material gave (Found: C, 73.56; H, 5.94; N, 1.72; Cl, 3.26. calc f r $TcC_{82}H_{72}NCl_2P_4B$: C, 71.57; H, 5.27; N, 1.02; Cl, 5.15%) and suggests contamination with BPh_4^-. The product could be recrystallised from CH_2Cl_2/MeOH.

Example 4

The preparation of $[Tc(NNPh)_2Cl(PPh_3)_2]$

Dry, distilled MeOH (5 cm^3) was added to a reaction flask containing a magnetic stirring bar, 222 mg PPh_3 (0.85 mmol) and 70 mg $[NBu_4][TcOCl_4]$ (0.14 mmol). This gave an orange suspension containing undissolved PPh_3. After five minutes 0.60 cm^3 of $PhNHNH_2$ (6.1 mmol) was added and the reaction mixture was heated to reflux for one hour. The solution was cooled to room temperature overnight and the resultant yellow-gold precipitate was collected, washed with MeOH (5 cm^3) and Et_2O (10 cm^3). The yield of $Tc(NNPh)_2Cl(PPh_3)_2$, after drying in vacuo, was 94 mg (0.11 mmol, 80%) based on technetium. This material is only partially soluble in halogenated solvents and insoluble in alcohols. Hence, attempts to purify the complex were only partially successful. Analysis calculated for $C_{48}H_{40}ClN_4P_2Tc$: 66.32% C; 4.64% H; 6.45% N. Found: 64.23% C; 4.28% H; 4.87% N.

Example 5

The preparation of $[Tc(NNPh)Cl(dppe)_2][PF_6]$

Method 1

52 µl of $PhNHNH_2$ (0.53 mmol) was added to a stirred solution of 80 mg $[NBu_4][TcOCl_4]$ (0.16 mmol) in 5 cm^3 MeOH. After five minutes 253 mg of dppe (0.64 mmol) was added as a solid to the stirred reaction mixture and this was then heated to reflux for one hour. The solution was cooled to room temperature, filtered, and an excess of NH_4PF_6 (1 g) in 3 cm^3 water was added to precipitate an orange

compound. This was collected, washed with MeOH (15 cm^3) and Et_2O (30 cm^3), and dried in the air. This gave 95 mg of product (0.08 mmol, 50%). The complex could be recrystallised from CH_2Cl_2/EtOH. Analysis calculated for $C_{58}H_{53}ClF_6N_2P_5Tc$: 58.97% C; 4.61% H; 2.37% N. Found: 58.92% C; 4.68% H; 2.70% N.

Method 2

A methanolic solution of $[NH_4][TcO_4]$ was prepared by adding 0.50 cm^3 of a 0.29 M aqueous solution of $[NH_4][TcO_4]$ (0.15 mmol) to 3.0 cm^3 of reagent grade MeOH. Phenyl hydrazine (50 µl, 0.51 mmol) was then added to this stirred solution. No reaction appeared to take place until 0.1 cm^3 of concentrated HCl was added to the reaction mixture five minutes later. This was immediately followed by the addition of 241 mg dppe (0.81 mmol) as a solid. The reaction mixture was heated to reflux for one hour, cooled to room temperature and filtered to remove excess, unreacted dppe. An excess of $[NH_4][PF_6]$ was added to the stirred solution as a solid and the resultant suspension was stirred at room temperature overnight. The orange precipitate was then collected, washed with ^iPrOH and Et_2O and dried *in vacuo* to give 108 mg of $[Tc(NNPh)(dppe)_2Cl][PF_6]$ (0.09 mmol, 60%). The product was identified by comparison of its IR and ^1H NMR spectra with those obtained from an authentic sample prepared by Method 1.

Example 6

The Preparation of $[Tc(NNC_6H_4Cl)(dppe)_2Cl][PF_6]$

This complex was prepared according to Method 2 above from $[NH_4][TcO_4]$ (0.19 mmol), 129 mg

trans-$ClC_6H_4NHNH_2.HCl$ (1.07 mmol), 0.1 cm^3 concentrated HCl, and 561 mg dppe (1.41 mmol). Yield of $[Tc(NNC_6H_4Cl)(dppe)_2Cl][PF_6]$: 298 mg, 0.24 mmol, 84%. Analysis calculated for $C_{58}H_{52}Cl_2F_6N_2P_5Tc.\frac{1}{2}CH_2Cl_2$: 55.99% C; 4.25% H; 2.23% N. Found: 55.73% C; 4.37% H; 1.93% N.

Example 7

The reaction of $[NBu_4][TcOCl_4]$ with Benzoylhydrazine and PPh_3

This reaction was performed according to the Method 1 above for the synthesis of $Tc(NNPh)_2Cl(PPh_3)_2$ using 77 mg $[NBu_4][TcOCl_4]$, 70 mg $PhC[O]NHNH_2$ (0.51 mmol) and 135 mg PPh_3 (0.51 mmol). After the reaction solution had been heated to reflux for one hour and cooled to room temperature, a light orange compound precipitated and was collected, washed with MeOH (15 cm^3) and Et_2O (30 cm^3) and then dried in the air. The compound was identified as $TcNCl_2(PPh_3)_2$ by comparison of its IR and NMR spectroscopic characteristics with those of an authentic sample.[8] The yield was 97 mg (0.14 mmol, 88%). Analysis calculated for $C_{36}H_{30}Cl_2NP_2Tc$: 61.12% C; 4.27% H; 1.98% N. Found: 60.66% C; 4.35% H; 2.32% N.

Example 8

The reaction between $[NBu_4][TcOCl_4]$, Benzoylhydrazine and dppe

This reaction was performed according to Method 1 above using 119 mg $[NBu_4][TcOCl_4]$ (0.24 mmol), 91 mg $PhC[O]NHNH_2$ (0.67 mmol), and 323 mg dppe

(0.81 mmol). The cooled reaction solution was filtered and an excess of $[NH_4][PF_6]$ was added with stirring. THe orange complex was identified as $[TcN(dppe)_2Cl][PF_6]$ by comparison of its spectroscopic properties with those of an authentic sample.[21] Yield: 196 mg (0.18 mmol, 75%). Analysis calculated for $C_{52}H_{48}ClF_6NP_5Tc$: 57.28% C; 4.44% H; 1.28% N. Found: 56.72% C; 4.84% H; 0.87% N.

Example 9

The reaction between $[NBu_4][TcOCl_4]$, H_2NNH_2 and dppe

This reaction was performed by Method 1 above using 124 mg $[NBu_4][TcOCl_4]$ (0.25 mmol), 15µl H_2NNH_2 (Aldrich, Anhydrous, 0.47 mmol) and 421 mg dppe (1.06 mmol). The reaction solution was heated to reflux for 30 minutes, cooled to room temperature, filtered and an excess of $[NH_4][PF_6]$ was added to the filtrate with stirring. The resultant orange-brown compound was collected by filtration. Yield: 144 mg (0.20 mmol, 80%). This product was identified as the complex $[TcN(dppe)_2Cl][PF_6]$.

Example 10

The Synthesis of $TcNNPhMe(PPh_3)_2Cl_3$

108 mg $[NBu_4][TcOCl_4]$ (0.22 mmol) was dissolved in 10 cm^3 dry MeOH and 52 µl $MePhNNH_2$ (0.44 mmol) was added to the stirred solution. The solution changed from pale green to red-orange immediately. 211 mg PPh_3 (0.80 mmol) was added to the reaction solution and the resulting suspension was heated to reflux for one hour. The resulting suspension was

cooled to room temperature and a large amount of a tan precipitate was collected, washed with MeOH (15 cm^3) and Et_2O (30 cm^3), and then dried in vacuo. The yield was 108 mg of a complex identified as $[Tc(NNPhMe)Cl_3(PPh_3)_2]$ (0.13 mmol, 59%). Analysis calculated for $C_{43}H_{38}Cl_3N_2P_2Tc$: 60.82% C; 4.51% H; 3.30% N; 12.53% Cl. Found: 60.01% C; 4.17% H; 3.53% N; 12.20% Cl.

Example 11

The Preparation of $[Tc(NNPhMe)Cl_2(PMe_2Ph)_3][PF_6]$

A red-orange solution was prepared by adding 0.10 cm^3 $MePhNNH_2$ (0.85 mmol) to a stirred solution of 1.47 mg $[NBu_4][TcOCl_4]$ (0.30 mmol) in 4.0 cm^3 of MeOH. 0.20 cm^3 of PMe_2Ph was then added to the reaction mixture and this was then heated to reflux for 45 minutes to give a clear orange solution. The solution was then concentrated to approximately 2 cm^3 and then 94 mg $[NH_4][PF_6]$ was added as a solid to the stirred reaction mixture. The precipitate which formed was collected and washed with 7:1 (v/v) Et_2O-^iPrOH. The filtrate was reconcentrated to give a second crop of gold-brown microcrystalline material. The yield was 138 mg of $[Tc(NNMePh)Cl_2(PMe_2Ph)_3][PF_6]$ (0.16 mmol, 54%). Analysis caluclated for $C_{31}H_{40}Cl_2F_6N_2P_4Tc$: 43.93% C; 4.76% H; 3.31% N. Found: 44.53% C; 5.22% H; 3.10% N.

Example 12

The Preparation of $[Tc^V(NNPhMe)Cl(Et_2NCS_2)_2]$

A red-orange solution was prepared as described above from 138 mg $[NBu_4][TcOCl_4]$ (0.28 mmol)

and 80µl $MePhNNH_2$ (0.68 mmol) in 3 cm^3 of MeOH. After this solution had been stirred at room temperature for five minutes, a solution of 200 mg $NaS_2CNEt_2.3H_2O$ (0.89 mmol) in 2 cm^3 MeOH. The resulting dark red solution was heated to reflux for 30 minutes, cooled to room temperature and the solvent was removed in vacuo to give a red, oily residue. This residue was taken up in 5 cm^3 of ^iPrOH and this suspension was filtered to give 73 mg of a pale brown powder which was washed with Et_2O. The filtrate was concentrated to about 1-2 cm^3 volume and 50 cm^3 Et_2O was added. The precipitated thus formed was collected and identical to the original material isolated. The overall yield of the complex, identified as $[Tc(NNMePh)Cl(Et_2NCS_2)_2]$ was 111 mg (0.02 mmol, 71%). The complex could be recrystallised from CH_2Cl_2/Et_2O. Analysis calculated for $C_{17}H_{27}ClN_4S_4Tc$: 37.12% C; 4.95% H; 10.19% N; 6.44% Cl. Found: 38% C; 5% H; 11% N; 9.4% Cl.

Example 13

The Reaction between $[NBu_4][TcOCl_4]$, $MePhNNH_2$ and dppe

An orange solution was prepared as described above from 100 mg $[NBu_4][TcOCl_4]$ (0.20 mmol), 45 µl $MePhNNH_2$ (0.38 mmol) in 4 cm^3 MeOH. 550 mg dppe (1.38 mmol) was then added to this stirred solution as a solid and the resultant suspension was heated to reflux for one hour, cooled to room temperature and filtered to remove unreacted dppe. An excess of $[NH_4][PF_6]$ was added as a solid to the filtered solution to give a tan precipitate which was washed with MeOH (20 cm^3) and Et_2O (10 cm^3). This yielded 121 mg of $[Tc(NH)O(dppe)_2][PF_6]$ (0.11 mmol, 55%). Analysis calculated for $C_{52}H_{49}F_6NOP_5Tc$: 58.27% C; 4.61% H; 1.31% N. Found: 56.90% C; 4.70% H; 1.61% N.

Example 14

The Reaction of $[NBu_4][TcOCl_4]$, Me_2NNH_2 and dppe

Method 1

An orange-red solution was prepared as described above from 211 mg $[NBu_4][TcOCl_4]$ (0.42 mmol), 35 µl Me_2NNH_2 (0.46 mmol) in 5 cm^3 MeOH and then 366 mg dppe (1.40 mmol) was added as a solid. The reaction mixture was heated to reflux for one hour, cooled to room temperature and a yellow precipitate was collected (72 mg of $[Tc(N_2)(dppe)_2Cl]$ (0.07 mmol, 17%). An excess of $[NH_4][PF_6]$ was added as a solid to the filtrate to give a gold-brown precipitate (137 mg) of $[Tc(NNMe_2)Cl(dppe)_2][PF_6]$ (0.12 mmol, 29%).

For $[Tc(N_2)(dppe)_2Cl]$

Analysis calculated for $C_{52}H_{48}ClN_2P_4Tc$: 65.17% C; 5.05% H; 2.92% N. Found: 64.70% C; 5.32% H; 2.07% N.

For $[Tc(NNMe_2)Cl(dppe)_2][PF_6]$

Analysis calculated for $C_{54}H_{52}ClF_6P_5Tc$: 57.33% C; 4.63% H; 2.48% N. Found: 51.6% C; 4.4% H; 1.8% N.

Method 2

A reaction solution was prepared as for Method 1 from 95 mg $[NBu_4][TcOCl_4]$ (0.19 mmol), 27 µl Me_2NNH_2 (0.36 mmol), 333 mg dppe (0.84 mmol) in 5 cm^3 MeOH. This reaction mixture was stirred at room

temperature for 70 hours. The reaction solution was filtered to remove excess dppe (no yellow precipitate was observed), 65 mg NH_4PF_6 (0.40 mmol) was added to the filtrate as a solid and the solution was then concentrated in vacuo and the residue was taken up in 5 cm^3 CH_2Cl_2. This solution was filtered to remove undissolved inorganic salts. After filtration, 25 cm^3 ^iPrOH was added to the filtrate to give 135 mg of a yellow-brown solid which was collected, washed and dried. This was identified by comparison of the IR spectrum of this complex with that of $[Tc(NNMe_2)Cl(dppe)_2][PF_6]$ prepared by Method 1 (0.12 mmol, 63%).

Example 15

The Reaction of $[NBu_4][TcOBr_4]$, Me_2NNH_2 and dppe

This was performed by Method 1 for the reaction described above for $[NBu_4][TcOCl_4]$ using 130 mg $[NBu_4][TcOBr_4]$ (0.20 mmol), 20 µl Me_2NNH_2 (0.26 mmol), 247 mg dppe (0.62 mmol) in 5 cm^3 MeOH. This gave 55 mg of a yellow complex, $Tc(N_2)Br(dppe)_2$ (0.06 mmol, 30%). No salts were isolated from the reaction filtrate after the addition of an excess of NH_4PF_6 to the solution. Analysis calculated for $C_{52}H_{48}BrN_2P_4Tc$: 62.22% C; 4.82% H; 2.79% N. Found: 58.48% C; 4.71% H; 2.03% N.

^{99m}Tc Complexes

General: The ^{99m}Tc diazenide and hydrazide (2-) complexes were prepared in a straightforward fashion from the appropriate hydrazine, $^{99m}TcO_4^-$ and a suitable ligand. The complex preparations were found

to yield the desired cationic products in reasonably high radiochemical purity (see Tables 2 - 4). The main contaminants in these preparations were the $[Tc^{III}Cl_2(L)_2]^+$ cations, as verified by comparison of HPLC and TLC characteristics of these impurities with authentic samples of these Tc^{III} species prepared by a literature method.[22] There is some question in the case of the $MePhNNH_2$ labelled species whether the complexes formed are of the formulation $[Tc^{IV}(NNMePh)Cl(L)_2]^+$ or $[Tc^{V}(NH)O(L)_2]^+$. Recent ICES studies on the preparation obtained from the labelling where L = P65 (mmmpe) have shown that the oxidation state of the complex obtained is +4.[23] This indicates that the species present in the $MePhNNH_2$ preparations are the desired hydrazido (2-) species.

Reagents: The ligands used are given in Table 1. All other reagents used were from commercial suppliers and used as received. $[^{99m}TcO_4]^-$ was obtained as solutions in physiological saline from Amertec II generators. Reaction products were analyzed by HPLC, TLC and gel electrophoresis as described elsewhere.[24] All preparations were performed under an atmosphere of nitrogen gas.

Example 16

Complex Preparation: 20-25 µl of hydrazine was added to 2 cm^3 of absolute ethanol, then $^{99m}TcO_4^-$ (0.2 - 3.0 GBq) and 10mg of ligand were added to the solution. This mixture was heated to 120°C for 30 - 60 minutes, cooled to room temperature and analyzed. For biodistribution studies the total volume of the preparation was made up to 5 cm^3 by the addition of sterile saline solution.

Animal Biodistribution Studies: Six male Sprague Dawley rats were injected while under light ether anaesthesia with 0.1 cm^3 of preparation (i.v., tail vein) and half were sacrificed by cervical dislocation while under ether anaesthesia at the appropriate time interval post-injection and dissected. Organs were weighed and their activities measured in an ionisation chamber. For the purposes of calculations blood was assumed to constitute 5.8% of the total body weight, muscle was assumed to be 43% and the lungs were assumed to weigh 1g.

Biodistribution results are given in Tables 2 - 4.

Table 1: Ligands used in ^{99m}Tc labelling work

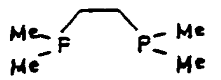
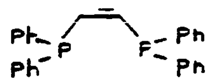
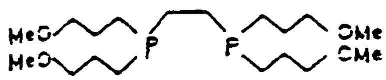
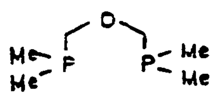
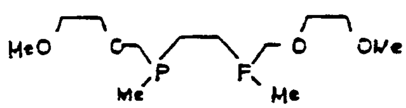
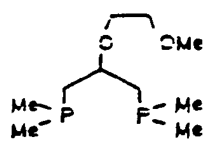
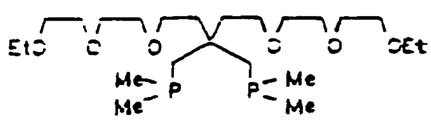
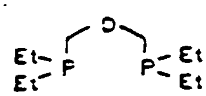
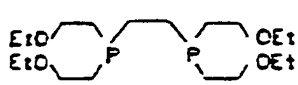
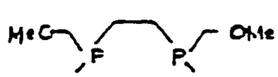
Abbreviation	Structure	Name
dmpe		1,2-bis(dimethylphosphino)ethane
dppe		1,2-bis(diphenylphosphino)ethane
P56		1,2-bis(di(3-methoxypropyl) phosphino)ethane
PL28		bis((dimethylphosphino)methyl)ether
P46		1,2-bis((2'-methoxy)ethoxymethyl) methylphosphino)ethane
PL34		1,3-bis(dimethylphosphino)-2-((2-methoxy)ethoxy)propane
PL38		1-3-bis(dimethylphosphino)-2,2-bis (2-(2-ethoxy)ethoxy)ethoxymethyl) propane; <u>or</u> 1,3-bis(dimethylphosphino)-2,2-bis (2,5,8-trioxadecyl)propane
PL31		bis((diethylphosphino)methyl)ether
P53		1,2-bis(di(2'-ethoxy)ethyl)phosphino ethane
P65		1,2-bis((methoxymethyl)methyl phosphine)ethane

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Table 1 (Continued)

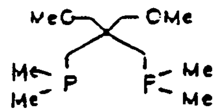
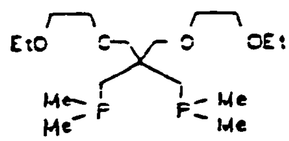
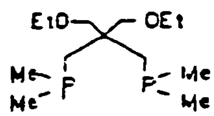
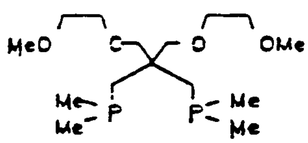
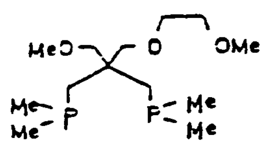
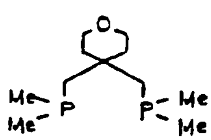
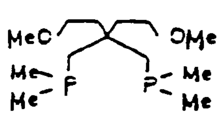
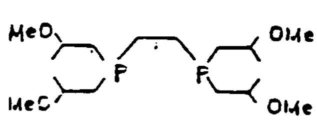
PL37		1,3-bis(dimethylphosphine)-2,2-bis (methoxymethyl)propane
PL40		1,3-bis(dimethylphosphino)-2,2-bis (2',5'-dioxaheptyl)propane
PL42		1,3-bis(dimethylphosphino)-2,2-bis (ethoxymethyl)propane
PL43		1,3-bis(dimethylphosphino)-2,2-bis ((2'-methoxy)ethoxymethyl) propane
PL46		1,3-bis(dimethylphosphino)-2-(methoxymethol)-2-((2'methoxy) ethoxymethyl) propane
PL49		4,4-bis((dimethylphosphino)methyl) tetrahydropyran
PL50		1,3-bis(dimethylphosphino)-2,2-bis (methoxyethyl)propane
P68		1,2-bis(di((2'methoxy)propyl) phosphino)ethane

Table 2: Biodistributions of Phenyldiazenide ^{99m}Tc species in Rats

Notebook	IV23		VI12		VI9	
Ligand	dmpe		PL28		P46	
RCP (%) MEK	60		84		80	
RCP (%) HPLC	40		70		75	
Time P.I.	2	60	2	60	2	60
Heart	0.91 (14)	0.78 (03)	1.12 (11)	0.65 (06)	0.96 (04)	0.80 (02)
Blood	6.98 (71)	1.10 (02)	4.18 (05)	0.46 (04)	7.45 (63)	1.01 (16)
Muscle	22.8 (3.0)	14.0 (3.7)	30.2 (3.0)	27.4 (3.6)	21.4 (3.1)	17.0 (4.0)
Lung	1.88 (14)	0.86 (10)	1.18 (14)	0.62 (05)	1.41 (27)	0.36 (05)
Liver	22.2 (2.6)	10.5 (8)	17.8 (2.9)	5.95 (57)	26.0 (1.0)	6.92 (1.23)
S.I.	13.2 (8)	36.7 (4)	13.2 (1.0)	39.6 (2.7)	11.0 (3.2)	44.0 (1.9)
Kidney	11.2 (8)	9.91 (1.25)	9.41 (0.30)	5.90 (06)	9.62 (48)	2.88 (16)
Bladder & Urine	0.11 (03)	11.3 (4)	0.11 (06)	10.9 (5.9)	0.11 (05)	17.8 (2.6)
Brain	0.06 (01)	0.02 (01)	0.04 (00)	0.02 (00)	0.05 (01)	0.01 (00)
H/Bl	1.97 (05)	9.52 (33)	3.97 (32)	21.3 (0.8)	2.05 (29)	13.2 (2.1)
H/Li	0.54 (11)	0.93 (11)	0.82 (19)	1.56 (12)	0.58 (06)	1.79 (30)

Table 2: Biodistributions of Phenyldiazenide ^{99m}Tc species in Rats (Continued-2)

Notebook	VI31		LH2.17		LH2.30	
Ligand	P46 (HPLC purified)		PL42		PL43	
RCP (%) MEK	50		65		26	
RCP (%) HPLC	50		70		50	
Time P.I.	2	60	2	60	2	60
Heart	1.05 (09)	0.96 (04)	1.22 (30)	1.19 (20)	0.55 (03)	0.26 (03)
Blood	7.00 (0.31)	0.78 (08)	28.6 (1.4)	8.99 (2.28)	21.5 (3.5)	1.14 (36)
Muscle	21.0 (3.1)	21.3 (2.3)	18.1 (0.5)	21.3 (0.3)	21.7 (2.4)	10.9 (1.3)
Lung	1.33 (14)	0.47 (05)	2.56 (33)	1.57 (32)	1.47 (04)	0.22 (03)
Liver	22.1 (2.0)	4.94 (77)	22.8 (3.2)	14.7 (1.6)	21.4 (1.6)	9.08 (2.03)
S.I.	11.5 (3.2)	39.8 (0.3)	7.66 (18)	31.8 (2.0)	8.6 (0.5)	45.6 (6.8)
Kidney	11.1 (2.1)	3.31 (17)	5.35 (46)	3.52 (47)	9.19 (74)	2.32 (32)
Bladder & Urine	1.01 (1.49)	17.0 (4.3)	0.06 (01)	2.61 (23)	·0.16 (06)	25.4 (4.6)
Brain	0.04 (00)	0.01 (00)	-	-	-	-
H/Bl	2.37 (12)	18.9 (1.6)	0.59 (12)	2.13 (43)	0.41 (06)	3.83 (1.03)
H/Li	0.66 (12)	2.77 (36)	0.73 (24)	1.12 (26)	0.38 (03)	0.40 (03)

Table 2: Biodistributions of Phenyldiazenide ^{99m}Tc species in Rats (Continued-3)

Notebook	LH2.51		PAH1.26		VI28	
Ligand	P65		PL50		PL38	
RCP (%) MEK	60		70		86	
RCP (%) HPLC	85		75		80	
Time P.I.	2	60	2	60	2	60
Heart	1.20 (11)	1.08 (09)	0.83 (09)	0.65 (04)	1.04 (06)	0.65 (09)
Blood	5.73 (58)	1.05 (09)	4.38 (25)	0.42 (03)	4.51 (1.36)	0.16 (02)
Muscle	27.8 (8.4)	23.6 (7.7)	18.7 (2.5)	14.9 (2.7)	21.0 (5.1)	16.2 (4.1)
Lung	1.61 (18)	0.53 (08)	1.02 (12)	0.43 (06)	1.41 (13)	0.35 (11)
Liver	22.0 (1.8)	6.68 (1.19)	34.8 (1.2)	4.35 (30)	28.4 (1.6)	9.27 (35)
S.I.	11.2 (2.1)	39.8 (4.3)	12.8 (0.7)	57.9 (2.4)	11.5 (2.0)	57.0 (2.8)
Kidney	12.0 (1.2)	3.71 (07)	12.0 (0.30)	6.81 (56)	10.7 (1.9)	4.01 (44)
Bladder & Urine	0.11 (0.05)	9.95 (66)	0.09 (03)	6.76 (65)	0.14 (04)	5.81 (1.46)
Brain	-	-	-	-	0.03 (00)	0.00 (00)
H/Bl	3.33 (30)	15.8 (1.0)	2.68 (22)	22.2 (0.4)	3.59 (88)	62.5 (7.0)
H/Li	0.81 (12)	2.33 (32)	0.31 (04)	1.27 (96)	0.48 (01)	1.05 (17)

Table 3: Biodistributions of $[Tc^{III}(NNC_6H_4NO_2)(Cl(dmpe)_2]^+$ in Rats

Notebook	CMAIV78	
Ligand	dmpe	
RCP (%) MEK	86	
RCP (%) HPLC	65	
Time P.I.	2	60
Heart	1.15 (22)	0.67 (05)
Blood	5.68 (66)	0.92 (07)
Muscle	26.2 (7.7)	16.8 (1.2)
Lung	2.27 (15)	1.04 (23)
Liver	22.4 (3.9)	12.3 (0.7)
S.I.	13.0 (3.1)	33.8 (3.2)
Kidney	9.47 (25)	9.47 (33)
Bladder & Urine	0.08 (02)	7.28 (1.10)
Brain	0.12 (00)	0.06 (00)
H/Bl	3.00 (49)	11.0 (0.9)
H/Li	0.72 (28)	0.76 (12)

Table 4: Biodistributions of ^{99m}Tc-hydrazide (2-) species in Rats and Guinea Pigs

Notebook	PAH2.14		CMAIV58		CMAVI41	
Ligand	P65		dmpe		dmpe (HPLC purified)	
RCP (%) MEK	86		78		83	
RCP (%) HPLC	90		70		73	
Time P.I.	2	60	2	60	2	60
Heart	0.95 (09)	0.69 (03)	1.13 (13)	0.80 (08)	1.25 (08)	0.99 (15)
Blood	4.77 (10)	0.69 (13)	7.84 (47)	1.05 (11)	7.95 (21)	1.05 (21)
Muscle	26.1 (5.8)	20.2 (2.7)	27.9 (4.9)	20.6 (3.2)	26.3 (5.2)	19.3 (4.9)
Lung	1.58 (0.36)	0.33 (02)	2.36 (37)	1.14 (07)	2.40 (0.21)	1.28 (20)
Liver	22.8 (1.4)	9.23 (26)	22.2 (0.6)	11.6 (1.6)	21.1 (1.7)	10.8 (1.9)
S.I.			10.5 (2.2)	30.6(3.4)	11.9 (3.2)	31.1 (4.5)
Kidney	7.76 (12)	1.95 (15)	9.95 (1.40)	11.1 (0.4)	10.8 (0.6)	11.6 (1.3)
Bladder & Urine			0.08 (01)	6.84 (77)	0.12 (07)	4.70 (93)
Brain			0.05 (01)	0.03 (01)	0.07 (01)	0.04 (01)
H/Bl	3.25 (27)	15.0 (3.4)	2.43 (12)	12.2 (1.4)	2.27 (21)	14.2 (2.4)
H/Li	0.64 (06)	1.11 (02)	0.78 (13)	1.06 (13)	0.82 (04)	1.30 (41)

Table 4: Biodistributions of ^{99m}Tc-hydrazide (2-) species in Rats and Guinea Pigs (Continued)

Notebook	CMAVI15		CMAVI36		CMAVI36
Ligand	P46		P46* (HPLC purified)		P46 (HPLC purified) RATS
RCP (%) MEK	64		54		54
RCP (%) HPLC	65		53		53
Time P.I.	2	60	2	60	60
Heart	0.81 (07)	0.58 (04)	0.96 (12)	0.65 (03)	0.97 (06)
Blood	7.10 (0.51)	0.50 (05)	10.1 (1.7)	0.89 (12)	0.27 (02)
Muscle	28.4 (2.5)	18.4 (2.5)	21.9 (3.3)	28.5 (2.2)	20.0 (1.2)
Lung	1.33 (09)	0.30 (07)	1.30 (05)	0.51 (11)	0.36 (10)
Liver	23.3 (0.5)	7.23 (70)	15.9 (1.1)	5.18 (36)	8.29 (67)
S.I.	9.38 (3.20)	44.8 (2.6)	11.3 (1.2)	15.0 (7.1)	43.6 (2.2)
Kidney	9.37 (52)	2.13 (10)	13.0 (1.6)	11.0 (0.3)	4.05 (66)
Bladder & Urine	0.18 (10)	19.2 (1.6)	0.22 (17)	10.6 (1.1)	12.7 (1.0)
Brain	0.04 (02)	0.51 (13)	-	-	-
H/Bl	1.65 (08)	16.5 (1.0)	2.89 (53)	17.8 (2.1)	58.7 (7.0)
H/Li	0.48 (03)	1.01 (13)	0.88 (10)	1.89 (0.22)	1.68 (14)

* In Guinea Pigs

Examples 17-19

All reactions were performed under an atmosphere of dinitrogen using predried, distilled solvents unless noted otherwise. $[Bu_4N][TcOCl_4]$ was prepared by the literature procedure.[28]

Example 17

Technetium Diazenido- Starting Materials

a) $[TcCl(NNC_6H_4Cl)_2(PPh_3)_2]$ 9

Method 1. From $[Bu_4N][TcOCl_4]$

$[Bu_4N][TcOCl_4]$ (0.134 g, 0.268 mmol), 4-$ClC_6H_4NHNH_2$.HCl (0.120 g, 0.67 mmol, 2.5 equivalents), Et_3N (0.09 ml, 0.67 mmol), and PPh_3 (0.211 g, 0.804 mmol, 3 equivalents) in dry methanol (5 ml) were stirred for 2 hours at room temperature. The khaki solid was collected by filtration, washed with methanol and ether and dried. (yield 0.134 g, 53%). The product could be recrystallised from CH_2Cl_2/MeOH yielding bright orange crystals. (Found: C,61.23; H,3.98; N,6.05; Cl,11.74. $TcC_{48}H_{38}N_4P_2Cl_3$ requires C,61.45; H,4.08; N,5.97; Cl,11.34 %). HPLC retention time 9.4 minutes, single species. $\nu_{max.}$ (KBr plates, nujol mull) 1600, 1555 cm^{-1} (NN). ^{31}P NMR

$(CDCl_3)$ 30.27 ppm singlet.

Method 2. From $[NH_4][TcO_4]$

Aqueous $[NH_4][TcO_4]$ (0.5 ml, 0.181 mmol) was evaporated to dryness *in vacuo*. $ClC_6H_4NHNH_2.HCl$ (0.142g, 0.793 mmol) in dry methanol (2.5 ml) was added with stirring to give an orange solution after 10 minutes. Solid PPh_3 (0.204 g, 0.778 mmol) was added and the mixture heated under reflux for 1.5 hours. After cooling to room temperature the khaki solid was collected by filtration and washed with ether (yield 0.113g, 67%). The product could be crystallised from CH_2Cl_2/MeOH to yield an orange crystalline solid which has an identical IR spectrum to an authentic sample of 9 prepared from $[TcOCl_4]^-$.

b) $[Tc(NNC_6H_4CH_3)_2(PPh_3)_2]$ 10

$[Bu_4N][TcOCl_4]$ (0.178 g, 0.356 mmol), $CH_3C_6H_4NHNH_2.HCl$ (0.282 g, 1.78 mmol, 5 equivalents), Et_3N (0.25 ml, 1.78 mmol), and PPh_3 (0.280 g, 1.07 mmol, 3 equivalents) were stirred in dry methanol (5 ml) overnight to give a khaki suspension. The product was collected by filtration, washed with ether and dried (yield 0.122 g, 40%). HPLC retention time 10.4 minutes, one major species. Analysis on the crude material gave (Found: C,64.1; H,4.6; N,5.9; Cl,3.53. $TcC_{50}H_{44}N_4P_2Cl$ requires C,66.93; H,4.94; N,6.24; Cl,3.95%). ^1H NMR $(CDCl_3)$ 2.29[6H, s, 2 x CH_3], 6.5-8.0 [38H, m, phenyl H]. ^{31}P NMR $(CDCl_3)$ 28.6 ppm singlet. $\nu_{max.}$ 1620, 1570, 1535 cm^{-1} (NN). The product may be recrystallised from CH_2Cl_2/MeOH.

c) $[TcCl_2(NNC_6H_4NO_2)(PPh_3)_2]$ <u>11</u>

$[Bu_4N[TcOCl_4]$ (0.152 g, 0.304 mmol), $O_2NC_6H_4NHNH_2$ (0.116 g, 0.76 mmol, 2.5 equivalents), and PPh_3 (0.239 g, 0.912 mmol, 3 equivalents) in dry methanol (5 ml) were stirred overnight to give a pale orange solid which was collected by filtration (yield 0.223 g, 77%). This was recrystallised from CH_2Cl_2/MeOH to give a lime-green solid (0.151 g, 52%). $v_{max.}$ 1620, 1600 (NN), 1555 (NO_2), 1335 (NO_2) cm^{-1}. ^1H NMR ($CDCl_3$) 3.4 [MeOH], 7.0-8.0[phenyl H]. ^{31}P NMR ($CDCl_3$) 30.0 ppm singlet. HPLC retention time 10.4 minutes. (Found: C,57.65; H,4.18; N,4.94; Cl,8.60. Found: C,57.42; H,4.24; N,4.95; Cl,7.95. $TcC_{43}H_{38}N_3Cl_2O_3P_2$ requires C,58.92; H, 4.37; N,4.79; Cl,8.09%).

<u>Example 18</u>

Substitution Chemistry of the Technetium Diazenido-Starting Materials

a) $[TcCl(NNC_6H_4Cl)(dppe)_2][BPh_4]$ <u>12</u>

<u>9</u> (0.098 g, 0.104 mmol) and dppe (0.104 g, 0.26 mmol, 2.5 equivalents) in methanol-toluene (1:1, 4 ml) were heated under reflux for 3 hours to give a dark orange solution. Solid $NaBPh_4$ (0.035 g, 1 equivalent) was added with stirring to precipitate an orange solid. The product was collected by filtration (yield 0.117 g, 77%). The crude product could be recrystallised from CH_2Cl_2/ether. (Found: C,70.55; H,5.34; N,2.17; Cl,4.72. $TcC_{80}H_{72}N_2BP_4Cl_2$ requires C,70.34; H,5.31; N,2.05; Cl,5.19%). HPLC retention time 14 minutes. $v_{max.}$ 1575, 1665 cm^{-1} (NN). ^1H NMR ($CDCl_3$) 2.68[8H, broad m, 2 x $-CH_2CH_2-$], 6.5-7.5[64H, broad unresolved m, phenyl H].

b) $[TcCl(NNC_6H_4Cl)(dppe)_2][PF_6]$ 12a

This was prepared in an analogous fashion to 12 using 9 (0.101 g, 0.107 mmol) and dppe (0.107 g, 0.269 mmol) in methanol/toluene (1:1, 4 ml) under reflux for 1 hour. $[NH_4][PF_6]$ (0.018 g, 0.110 mmol) was added with stirring to the filtered reaction mixture to give 12a (yield 0.059 g, 43%). This could be recrystallised from CH_2Cl_2/MeOH (Found: C,55.44; H,4.27; N,2.48; Cl, 6.35. $TcC_{58}H_{44}N_2P_5Cl_2F_6$ requires C,57.68; H,3.67; N,2.32; Cl,5.87%).

c) $[TcCl(NNC_6H_4NO_2)(dppe)_2][BPh_4]$ 13

11 (0.051 g, 0.06 mmol) and dppe (0.060 g, 0.151 mmol, 2.5 equivalents) in methanol/toluene (1:1, 3ml) were heated under reflux for 1 hour to give an orange-red solution. After cooling to room temperature solid $NaBPh_4$(0.02 g, 1 equivalent) was added with stirring to precipitate the product as an orange solid. This was collected by filtration and washed with MeOH and Et_2O (yield 0.06 g, 72%). The product was recrystallised from CH_2Cl_2/Et_2O (yield 0.042 g, 50%) as an orange crystalline solid. $\nu_{max.}$ 1645s, 1600w (NN), 1570 (NO_2), 1340 (NO_2') cm^{-1}. HPLC retention time 14.2 minutes, single peak. (Found: C,67.65; H,5.12; N,2.93; Cl,4.14. $TcC_{82}H_{72}N_3O_2Cl$-$P_4B.1/2CH_2Cl_2$ requires C,68.66; H,5.10; N,2.91; Cl,4.91%).

d) $[Tc(NNC_6H_4Cl)(S_2CNMe_2)_2(PPh_3)]$ 14

9 (0.139 g, 0.148 mmol) and NaS_2CNMe_2 (0.08 g, 0.444 mmol, 3 equivalents) in absolute ethanol (2 ml) were heated under reflux for 1.5 hours. The orange solid was collected by filtration after cooling (yield 0.072g) and redissolved in CH_2Cl_2 before passage down a Fluorsil column eluting the orange band with CH_2Cl_2. This eluate was evaporated to dryness and the residue recrystallised from CH_2Cl_2/Et_2O to give dark orange crystals (yield 0.072 g, 66%). HPLC retention time 13.6 minutes, single species. (Found: C,45.82; H,4.09; N,6.79; Cl,6.25. Found: C,45.99; H,4.04; N,6.77. $TcC_{30}H_{31}N_4ClS_4P.1/2CH_2Cl_2$ requires C,46.74; H,4.11, N,7.15; Cl,9.05. $TcC_{30}H_{31}N_4ClS_4P.1/4CH_2Cl_2$ requires C,47.65; H,4.16, N,7.35; Cl,6.97%). ^1H NMR ($CDCl_3$) 2.92[3H, s, CH_3], 3.06[3H, s, CH_3], 3.31[3H, s, CH_3], 3.39[3H, s, CH_3], 5.27[CH_2Cl_2], 6.8-7.7[19H, m, phenyl H]. ^{31}P NMR ($CDCl_3$) no signal was observed in this sample at room temperature.

e) $[TcCl(NNC_6H_4Cl)(maltol)(PPh_3)_2]$ 15

9 (0.145 g, 0.155 mmol) and maltol (0.059 g, 0.465 mmol, 3 equivalents) in absolute ethanol (2 ml) were heated under reflux for 2 hours. After cooling to room temperature the orange product was collected by filtration and washed with ethanol. The product was recrystallised from CH_2Cl_2/ether (yield 0.03 g, 21%) as dark orange crystals. (Found: C,59.68; H,4.11; N,3.03; Cl,7.73. $TcC_{48}H_{39}N_2Cl_2O_3P_2$ requires C,62.41; H,4.23; N,3.03, Cl,7.68%). $\nu_{max.}$ 1615s, 1560 cm^{-1}. ^1H NMR ($CDCl_3$) 2.21[3H, s, CH_3], 5.63[1H, d, J^3_{HH} = 4 Hz, C=CH], 6.92[1H, d, J^3_{HH} = 4 Hz, C=CH], 7.0-8.0[34H, m phenyl H]. ^{31}P NMR ($CDCl_3$) 30.0 ppm singlet. HPLC retention time 10 minutes.

f) $[Tc(NNC_6H_4Cl)(salen)(PPh_3)]$ 16

9 (0.100 g, 0.107 mmol), salenH_2 (0.032 g, 0.119 mmol, 1.1 equivalents), and Et_3N (0.40 ml, 0.259 mmol, 2.2 equivalents) in dry methanol/toluene (1:1, 3 ml) were heated under reflux for 2 hours. After cooling, addition of ether gave a khaki-green solid which was collected by filtration, washed with ether and dried (yield 0.052 g, 63%). The product could be recrystallised from CH_2Cl_2/heptane as very dark green crystals. (Found: C,61.77; H,4.41; N,7.17; Cl,4.77. $TcC_{40}H_{33}N_4PO_2Cl$ requires C,62.63; H,4.34; N,7.30; Cl,4.62%). $\nu_{max.}$ 1600, 1610, 1620 (NN), 1540 (C=N) cm^{-1}. ^1H NMR ($CDCl_3$) 4.0[4H, broad m, $-CH_2CH_2-$], 6.0-7.6[27H, broad m, phenyl H], 8.14[2H, s, N=CH]. ^{31}P NMR ($CDCl_3$) no signal was observed at room temperature. HPLC retention time 11.6 minutes.

g) $[Tc(NNC_6H_4Cl)_2(N_2S_2)]_x$ 17
N_2S_2 = $(HSCH(Me)CONHCH_2-)_2$

9 (0.083 g, 0.088 mmol), N_2S_2 (0.023 g, 0.097 mmol, 1.1 equivalents), and Et_3N (0.05 ml, 0.34 mmol, 4 equivalents) in dry methanol (2 ml) were heated under reflux for 1 hour to give a dark brown-green solution. The solvent was removed *in vacuo* and the brown oil triturated with isopropanol to give a dark brown solid product (yield 0.011 g). The product was too insoluble for satisfactory recrystallisation and analysis by NMR, but appeared to be diamagnetic. HPLC retention time 12.2 minutes. (Found: C,40.36; H,4.40; N,9.19; Cl,11.97. $TcC_{20}H_{24}N_4Cl_2S_2O_2$ requires C,40.96; H,4.12; N,9.55; Cl,12.09%).

Example 19

Technetium Imido Complexes

$[TcCl_2(NC_6H_4CO_2)(PPh_3)_2]$ 18

Method 1. From $[NH_4][TcO_4]$

Aqueous $[NH_4][TcO_4]$ (1 ml, 0.343 mmol), $2\text{-}HO_2CC_6H_4NH_3Cl$ (2-carboxyaniline hydrochloride) (0.298 g, 1.715 mmol, 5 equivalents), and PPh_3 (0.360g, 1.372 mmol, 4 equivalents) in reagent grade methanol (10 ml) were stirred overnight to give a bright green precipitate. The product was collected by filtration, washed with MeOH, ether and dried in vacuo (yield 0.139 g, 50%). (Found: C,63.30; H,4.44; N,1.77. $TcC_{43}H_{34}NO_2P_2Cl_2$ requires C,62.33; H,4.14; N,1.67%). The product was soluble in DMF and CH_2Cl_2.

Method 2. From $[Bu_4N][TcOCl_4]$

$[Bu_4N][TcOCl_4]$ (0.262 g, 0.525 mmol), anthranilic acid (0.72 g, 5.25 mmol, 10 equivalents), and PPh_3 (0.48 g, 1.84 mmol, 3.5 equivalents) in absolute ethanol (20 ml) were heated under reflux for 2 hours. The hot solution was filtered (air) and taken to dryness in vacuo. The residue was then triturated with ether and the solid green product isolated after filtration was recrystallised from EtOH/hexane (yield 0.114 g, 26%). ^{31}P NMR (DMSO) 31.2 ppm singlet.

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CLAIMS

1. A complex of technetium (^{99}Tc or ^{99m}Tc) which contains the moiety Tc=NR, Tc-N=NY or $Tc(-N=NY)_2$, and a ligand which confers biological target-seeking properties on the complex,

wherein R represents an aryl group, a substituted or unsubstituted alkyl group, or the grouping $=NR^1R^2$;

Y represents an aryl group or a substituted or unsubstituted alkyl group;

and R^1 and R^2 are hydrogen, aryl groups or substituted or unsubstituted aliphatic or cyclic alkyl groups, and may be both the same or different, provided that both are not hydrogen.

2. A complex as claimed in claim 1 of the formula $L_nTc=NR$,

wherein L represents a mono-dentate or multi-dentate ligand;

n is 1, 2, 3 or 4;

and R is as previously defined.

3. A complex as claimed in claim 1 of the formula $L_nTc-N=NY$,

wherein L represents a mono-dentate or multi-dentate ligand;

n is 1, 2, 3 or 4;

and Y is as previously defined.

4. A complex as claimed in claim 1 of the formula $L_nTc(-N=NY)_2$,

wherein L represents a mono-dentate or multi-dentate ligand;

n is 1, 2, 3 or 4;

and Y is as previously defined.

5. A complex as claimed in any one of claims 1 to 4, wherein the alkyl group is substituted with oxygen, nitrogen, sulphur and/or phosphorus.

6. A complex as claimed in any one of the preceding claims, wherein the ligand is selected from phosphines and arsines of the general formula

$$Q_2B(CD_2)_nBQ_2,$$

wherein Q represents hydrogen, an aryl group or a substituted or unsubstituted alkyl group;

B is P or As;

(CD_2) is a substituted or unsubstituted methylene group;

and n is 1, 2, 3 or 4.

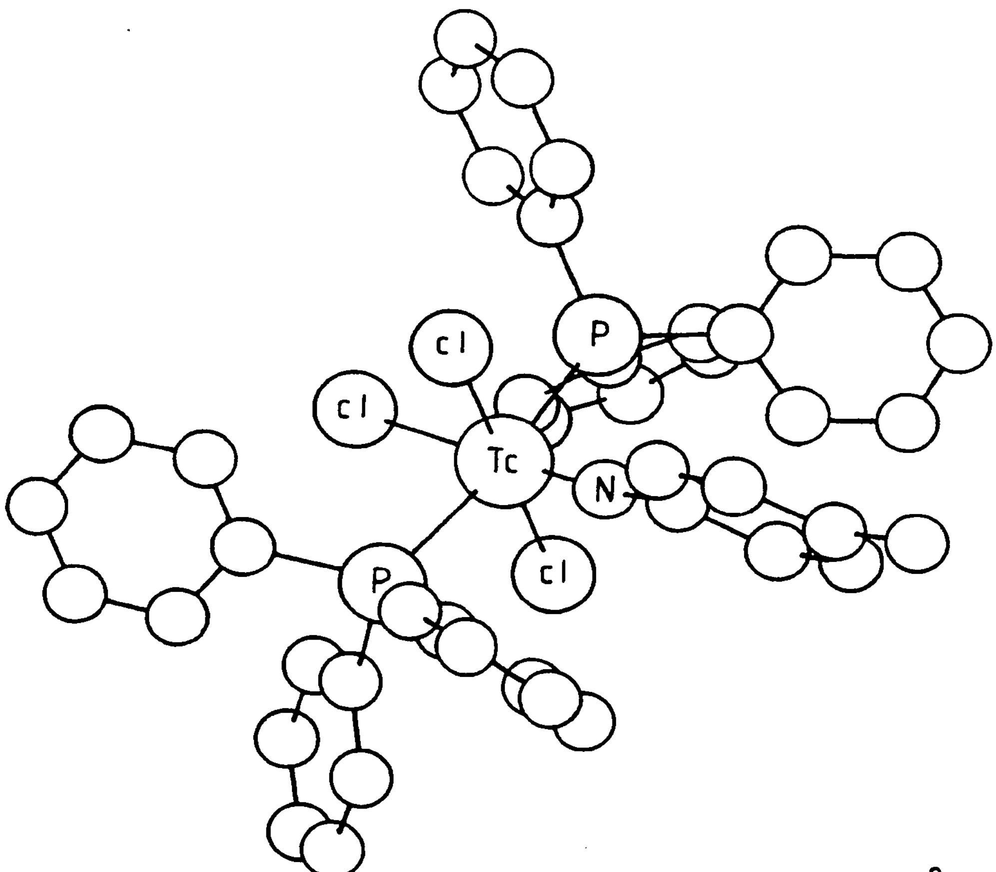
7. A complex as claimed in any of the preceding claims, useful as a radiopharmaceutical, wherein the biological target-seeking properties of the complex are determined by the nature of the ligands present and/or of the substituents R and Y.

8. A method of preparing a complex of technetium (^{99}Tc or ^{99m}Tc) which contains the moiety Tc=NR, Tc-N=NY or $Tc(-N=NY)_2$, wherein R and Y are as defined in claim 1, which method comprises the derivatisation of a technetium oxo-containing species by condensation with a hydrazine, an amine, an isocyanate, a sulphinylamine or a phosphinimine.

9. A method of preparing a complex of technetium (^{99}Tc or ^{99m}Tc) which contains the moiety Tc=NR, Tc-N=NY or $Tc(-N=NY)_2$, wherein R and Y are as defined in claim 1, which method comprises the reaction of a hydrazine or amine with a complex containing technetium-halogen bonds.

10. A radiopharmaceutical which includes a complex of technetium as claimed in any one of claims 1 to 7.

Fig 1 Pluto Plot of $[Tc(Ntol)Cl_3(PPh_3)_2]$



Tc – N, 1·7Å
Tc – N-C, 168Å

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 90/01330

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC^5: A 61 K 49/02, C 07 B 59/00

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC^5	A 61 K, C 07 B, C 07 F

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [*]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
P,X	Polyhedron, volume 9, no. 12, June 1990, Pergamon Press Plc., (Oxford, GB), A.M. Archer et al.: "Development of new technetium cores containing technetium-nitrogen multiple bonds. Synthesis and characterization of some diazenido-. hydrazido- and imido-complexes of technetium", pages 1497-1502 see the whole article (cited in the application) --	1-10
P,X	Inorg. Chem., volume 28, 4 October 1989, American Chemical Society, (Washington, DC, US), T. Nicholson et al.: "Synthesis, spectroscopy, and structural characterization of five-coordinate, Bis (aryldiazenido)technetium complexes and their protonation reactions. X-ray structure of $TxCI(PPh_3)_2(NNC_6H_4BR)_2$ ", ./.	1-10

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
9th January 1991	06 FEB 1991
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	MISS T. TAZELAAR

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III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages	Relevant to Claim No.
	pages 3813-3819 see page 3813, summary; pages 3815-3816, results and discussion --	
Y	Nouveau Journal de Chimie, volume 1, no. 6, (Montreux, FR), D.L. DuBois et al.: "Diazenido, dinitrogen and related complexes", pages 479-492 see page 479; abstract; page 483; pages 488-489 --	1-10
Y	Journal of Radioanalytical and Nuclear Chemistry, Articles, Volume 102, no. 2, 1986, Elsevier Sequoia S.A., (Lausanne, CH), S. Abram et al.: "Lipophilic technetium complexes. IV neutral. lipid-soluble technetium complexes with dithioligands containing T0=O and Tc=N cores an in vitro study", pages 309-320 see pages 309-311, introduction (cited in the application) --	1-10
Y	J. Chem. Soc. Chem. Commun., 1970, (London, GB), I.S. Kolomnikov et al.: "Phenyl isocyanate as a source of phenylimido-ligand", page 1432 see the whole article (cited in the application) --------	1-10